Remarks

In the Office Action, the Examiner noted that claims 1, 3, 6-9, 11-23, 25-33 and 35 are pending in the application; and that claims 1, 3, 6-9, 11-23, 25-33 and 35 are rejected. By this amendment, claim 13 has been amended. Thus, claims 1, 3, 6-9, 11-23, 25-33 and 35 are pending in the application. No new subject matter has been inserted through these amendments. Specifically, by way of this amendment an inadvertent spelling error in claim 13 has been corrected by deleting the word "compromising" and inserting therefor "comprising." Therefore, it is submitted that all of the amendments are fully supported by the specification. The Examiner's rejections are respectfully traversed below.

Withdrawal of Outstanding rejections

Applicants note with much appreciation withdrawal of all of the outstanding rejections in the previous Office Actions, however new grounds of rejections have been issued in this Office Action.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 13 and 23 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner has noted that "Claim 13 is confusing because the dosage form is "compromising," and it is uncertain how the dosage form "compromises." However, as noted above this was an inadvertent spelling error in that the word "compromising" should have been "comprising" and such a correction has been made in this amendment, and therefore, it is submitted that claim 13, as amended, fully satisfy the requirement of 35 U.S.C. § 112, second paragraph.

Additionally, the Examiner alleges that "Claim 23 depends on claim 20, which in the line of dependencies goes back to claim 1, which is directed to a coated dosage form that contains active agent in the matrix. It is thus unclear how the claim 23 does not

contain active agent in the matrix. Claim 23 is not rejected over art in view of the indefiniteness of the claim." Applicants submit that this is an improper analysis of the claims.

In particular, the Examiner's attention is drawn to involved claims 23, 20, 35, 14, 13, 3 and 1, which are reproduced below for the convenience of the Examiner:

Claim 23. (Original) A tablet according to claim 20 wherein the matrix is free of active substance.

Claim 20. (Previously presented) A tablet according to claim 35 wherein the delayed release coated core in the form of a particle, pellet, bead granule or spheroid having a diameter of 0.3 to 3 mm is imbedded in a rapidly disintegrating matrix.

Claim 35. (Previously presented) A pharmaceutical dosage form according to claim 14 wherein the delayed release coated core is combined with a sustained release entity or immediate release entity.

Claim 14. (Previously presented) A pharmaceutical dosage form according to claim 13 in the form of a tablet, a multilayer tablet, a multicoated tablet or a capsule.

Claim 13. (Currently amended) A pharmaceutical dosage form ~~compromising~~ **comprising** a delayed release coated core according to Claim 3.

Claim 3. (Previously presented) A delayed release coated core according to claim 1 wherein the ammonio methacrylate copolymers are of type A or B.

Claim 1. (Previously presented) A delayed release coated core which produces a timed pulse release containing an active substance in its core and a polymer coating comprising an ammonio methacrylate copolymer, said core further containing a zwitterionic surfactant in an amount of from 10% to 50% relative to the amount of ammonio methacrylate copolymer in the coating, and wherein the zwitterionic surfactant is chosen from N-alkylbetaines, C-alkylbetaines, N-alkylamidobetaines and N-alkylglycines.

From the foregoing recitations of involved claims, it is clear that the delayed release coated core is comprised of an active substance as specifically recited in claim 1. Claim 3

which depends upon claim 1 provides only further limitation of ammonio methacrylate copolymers of type A or B. Claim 13 which depends on claim 3 provides only a further limitation of pharmaceutical dosage form comprising delayed release core. Claim 14 further limits such pharmaceutical dosage forms in the form of tablet, a multilayer tablet, etc. Claim 35 provides for a limitation wherein the pharmaceutical dosage form comprises delayed release coated core in combination with either a sustained release entity or immediate release entity. Claim 20 further recites a tablet having the delayed release core in the form of a particle, pellet bead granule or spheroid imbedded in a rapidly disintegrating matrix. Finally claim 23 recites the limitation of said matrix free of active substance.

From the foregoing it is submitted that the active substance is always in the delayed release coated core as recited in claim 1 and all of the dependent claims therefrom incorporate this limitation as delineated above and recite only further limitations. Therefore it is submitted that Examiner's confusion as to matrix containing the active substance is not only unsubstantiated but also of no merit. It should again be pointed out that the delayed release core containing the active substance in the form of particle, pellet, etc, is dispersed throughout a matrix in accordance with claim 20. Therefore there is no need for the active substance in the matrix as specifically recited in claim 23. Accordingly it is submitted that claim 23 as recited is not indefinite and therefore fully satisfy the requirements of 35 U.S.C. § 112, second paragraph.

In view of all of the arguments advanced above, it is respectfully requested that the rejection as to claims 13 and 23 be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

There are a total of four separate rejections under this section based on 8 different references as set forth below. Applicants are consolidating the arguments based on these rejections as it appears that all of these rejections are non-meritorious and it is apparent from the discussions that follow do not establish prima facie obviousness. Accordingly, it is respectfully requested that each of the arguments presented below shall be taken into

consideration carefully in determining patentability of claims 1, 3, 6-9, 11-23, 25-33 and 35, and all of the rejections be withdrawn as done from our earlier response of March 24, 2007.

Claims 1 and 6 stand rejected under 35 USC 102(e) as anticipated by or, in the alternative, under 103(a) as obvious over Bradbury et al. (US 6,124,362).

First of all, Applicants submit that Bradbury is not available as a prior art reference under 35 U.S.C. § 103(a) because the instant application claims priority to European Application 99401606.1, filed June 28, 1999, whereas Bradbury was published only on September 26, 2000, almost fifteen months after the priority date of the instant application. Thus on this basis alone rejection as to claims 1 and 6 should be withdrawn.

Additionally, the Examiner has not established prima facie case of obviousness as to instant claims 1 and 6 based on the teachings of Bradbury. In other words, it is submitted that claims 1 and 6 are patentably distinguishable from Bradbury for the reasons advanced below, and therefore, it is respectfully requested that rejection as to claims 1 and 6 be withdrawn.

Specifically, as we already noted above claim 1 recites a delayed release coated core containing an active substance in its core. More specifically, claim 1 recites as follows:

> Claim 1. (Previously presented) A delayed release coated core which produces a timed pulse release containing an active substance in its core and a polymer coating comprising an ammonio methacrylate copolymer, said core further containing a zwitterionic surfactant in an amount of from 10% to 50% relative to the amount of ammonio methacrylate copolymer in the coating, and wherein the zwitterionic surfactant is chosen from N-alkylbetaines, C-alkylbetaines, N-alkylamidobetaines and N-alkylglycines.

Thus there are at least four major operative elements in claim 1 which are as set forth below:

a) A delayed release coated core which produces timed pulse release containing an active substance;

b) A polymer coating comprising an ammonio methacrylate copolymer;

c) Said core also comprising a zwitterionic surfactant in certain amounts; and

d) Said surfactants chosen from N- or C-alkylbetaines, N-alkylamidobetaines and N-alkylglcines.

Bradbury on the other hand discloses and claims a topical composition for hair growth, see specifically claim 1 of Bradbury. This is in fact the central focus of this invention. Additionally, Bradbury broadly does disclose use of certain surfactants in its compositions. However, there is no where in Bradbury a disclosure of delayed release coated core which produces timed pulse release containing active substances. Furthermore, there is no teaching of any polymer coatings suitable for use in the timed pulsed delivery of active substances as presently disclosed and expressly claimed in claim 1.

Thus it is submitted that Bradbury neither teaches nor suggests one of ordinary skill in the art to modify Bradbury so as to arrive at the claimed invention as recited in claim 1 at the time Applicants made this invention.

The Office has set new guidelines for the Examiners to determine whether or not the claim under review is obvious over the cited prior art. See specifically, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in view of the Supreme Court Decision in KSR International Co. v. Teleflex Inc., October 10, 2007. It is clearly sated there that an Examiner provide articulated reasons for the factual determinations underlying an asserted prima facie case of obviousness, which is consistent with the rule set out in KSR. However, as we noted above, the Examiner has clearly not provided any factual reasons why Bradbury would have led one of ordinary skill in the art to arrive at Applicants' invention at the time Applicants made this invention. Instead, the Examiner notes the following in reference to the teachings of Bradbury:

"Bradbury teaches a composition that can be administered topically, orally or parenterally (column 5, lines 45-55); the composition comprises triterpenes (columns 6 and 7) such as betulinic acid (column 7, lines 37-54; column 8, lines 46-65; column 9, lines 12-26 and Examples 6 and 7) and carrier vehicle such as

water, lipophilic or hydrophilic emollients/humectants, surfactants, thickeners, powders, polymers, resins, plasticizers, fillers, lubricants, binders, disintegrants, solvents, co-solvents, buffer systems, preservatives, sweetening agents, flavoring agents, pharmaceutical grade dyes and pigments (column 12, lines 41-46). Surfactants are desirable and used at levels of 0.1% to 30% and the surfactants are anionic, cationic, non-anionic or amphoteric or combinations (column 15, lines 59-65) and the amphoteric surfactants encompassing zwitterionic surfactants (column 18, lines 27-29). Examples of amphoteric or zwitterionic surfactants used in the composition of Bradbury are the betaines and cocamidopropyl betaine is specifically named (column 18, lines 50-64). The polymers preferred for use in the composition are HPMC alone or in combination with carboxymethylcellulose, acrylic resins, ethylcellulose and polyvinylpyrrolidone (column 22, lines 50-57). The composition also optionally contains enhancers at levels of 0.01% to about 15% (column 22, line 61 to column 23 line 3). Non-steroidal anti-inflammatory actives (NSAIDs) (column 23, lines 57-63) such as acetyl salicylic acid, ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, tioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen and bucloxic acid (column 26, lines 6-11) are useable in the composition. The composition is prepared by mixing the ingredient together. The instant application uses solution of polymer to coat the drug according to page 12, lines 8-13), which reads on mixing the drug with suspension or solution containing the polymer, flavoring agents or fillers (columns 29 and 30) and in the process the active agents, betulinic acid and other actives such as NSAID are coated with the carrier vehicle. Therefore, Bradbury teaches coated drugs, which the coating comprising polymer and surfactants such as the betaine surfactants meeting the requirements of claims 1. Cocamidopropyl betaine, a specific named betaine meets claim 6; delayed release is achieved by the type of the polymer associated with the drug/active in the composition and in the is case, the presence of acrylic type polymer such as the EUDRAGIT polymers meet that

limitation. In the alternate, specific zwitterionic surfactants are named by Bradbury to include betaines (column 18, line 48) and specific betaines such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alpha-carboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, cetyl dimethyl betaine (available as Lonzaine 16SP from Lonza Corp.), lauryl bis-(2-hydroxyethyl) carboxymethyl betaine, oleyl dimethyl gammacarboxypropyl betaine, lauryl bis-(2-hydroxypropyl)alpha-carboxyethyl betaine, coco dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl) sulfopropyl betaine, amidobetaines and amidosulfobetaines (wherein the $RCONH(CH_2)_3$ radical is attached to the nitrogen atom of the betaine), oleyl betaine (available as amphoteric Velvetex OLB-50 from Henkel), and cocamidopropyl betaine (available as Velvetex BK-35 and BA-35 from Henkel named are named (column 18, lines 50-64). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made use any of the betaine surfactants named in Bradbury either as an emulsifying agent or thickener or as surfactant that does not irritate the skin or mucous membrane.

From the foregoing it is clear that what the Examiner has done is to summarize the disclosures of Bradbury instead of "a finding that the prior art included each element claimed in the instant invention" as required by the KSR court. More specifically, as we noted above, Bradbury does not disclose a key element of "delayed release coated core which produces a timed pulse release containing an active substance in its core" as specifically taught and claimed in the instant invention in claim 1. Therefore, it is respectfully submitted that Bradbury is not only NOT available as a prior art but also Bradbury DOES NOT render claim 1 obvious.

Similarly, dependent claim 6, which depends directly upon claim 1, further recites a limitation of the zwitterionic surfactant to be cocamidopropylbetaine, and therefore, claim 6 is also patentably distinguishable from Bradbury.

In view of the foregoing, it is respectfully requested that rejection as to claims 1 and 6 be withdrawn.

Claims 1, 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bradbury et al. (US 6,124,362) in view of Morella et al. (US 6,197,348).

As we already noted above Bradbury is not available as a prior art. In addition, as we convincingly argued above Bradbury neither discloses nor suggests a "delayed release coated core which produces a timed pulse release containing an active substance in its core" as specifically recited in claim 1. Furthermore, dependent claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 depend directly or indirectly upon claim 1 and further recite additional limitations. Since we have already shown that the independent claim 1 is non-obvious over Bradbury, naturally, all of dependent claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 are also non-obvious over Bradbury.

As to Morella, it is also not available as a prior art because the present application claims priority to European Application 99401606.1, filed June 28, 1999, whereas Morella was published only on March 6, 2001, almost twenty months after the priority date of the instant application. In fact, the corresponding PCT application, WO01/00182 was published on January 4, 2001, three months prior to the issuance of Morella. Thus on this basis alone rejection as to claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 should be withdrawn.

In addition, it is again submitted that claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 are patentably distinguishable from that of Morella. In fact, Morella not even remotely teach or suggest "delayed release coated core which produces a timed pulse release containing an active substance in its core" as specifically taught and claimed in the instant claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35.

In particular, Morella teaches and discloses a taste masked liquid suspensions particularly suspensions of microcapsules wherein taste is masked by a polymer coating. Thus it is submitted again that one of ordinary skill in the art would not be motivated from these teachings to prepare pulsed release formulations specifically incorporating the "delayed release coated core which produces a timed pulse release containing an active substance in its core" as taught by the present invention, this satisfying the guidelines

discussed above in support of non-obviousness. It is further submitted that the Examiner has again not articulated why Bradbury in view of Morella would have led one of ordinary skill in the art to arrive at the instant invention.

In view of the foregoing, it is respectfully submitted that rejection as to claims 3, 6, 7, 9, 13, 14, 16, 18, 29-32 and 35 be withdrawn.

Claims 1, 3, 6-9 and 11-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Heinicke et al. (US 5,834,024) in view of Baichwal et al. (US 5,478,574) and further in view of Niemiec et al. (US 2002/0077256 A1).

Again, Applicants submit that Niemiec et al was published only on June 20, 2002, whereas the present application with a filing date of December 20, 2001 claims priority to European Application 99401606.1, filed June 28, 1999. Therefore, Niemiec is not available as a prior art reference.

In addition, the Examiner alleges that "Heinicke discloses a diltiazem tablet formulation comprising a core that is a sphere, bead or seed of an inert ingredient and the core comprises a pharmaceutical (diltiazem), a binder, emulsifier or stabilizer and the core may further include a dispersing agent, glidant and/or surfactant (column 4, lines 27-49). In example 1, the core is made up of diltiazem, hydroxypropylcellulose and sugar spheres, the core coated with EUDRAGIT RL and EUDRAGIT RS. Regarding the delayed nature of the instant formulation as recited in claim 1, the formulation of the prior art would also be a delayed release composition since the prior art teaches the same polymers and would thus inherently produce a timed pulse release of the active agent. The presence of the hydroxypropylcellulose separates diltiazem from the polymer coating layer meeting claim 11. The EUDRAGIT RL (type A) and/or EUDRAGIT RS (type B) coated dosage form meets claim 3. Claims 15-17 are product by process claims while claim 18 recites properties of the dosage form so that the Heinicke dosage from meets claims 15-18. Heinicke tablet dosage form comprising a core that is sphere, bead or seed of an inert ingredient and the core comprises a pharmaceutical (diltiazem) and meets claims 8 and 9, and in the absence of factual evidence, the particle size recited in claim 8 is not inventive over a generic teaching of

particles in the prior art.

However, while Heinicke describes a dosage form that contains generic surfactant, Heinicke does not describe the surfactant as amphoteric/zwitterionic or non-ionic or ionic. But, Baichwal describes controlled release dosage form that is a tablet or capsule or pellet (column lines 1-5); Baichwal formulates the dosage form using a wide variety of pharmaceutically active agents (column 11, lines 1 and 2); diltiazem is a named vasodilator in Baichwal (column lines 14 and 15); the dosage form contains wetting agent or surfactants in from about 1 to about 10% or higher by weight (column 8, lines 26-39); the surfactant is anionic or cationic or non-ionic or amphoteric/amphipathic/amphophilic (column 8, lines 4-52); suitable amphoteric/amphipathic/amphophilic surfactants are N-substituted alkyl amides, N-alkyl betaines, sulfobetaines and N-alkyl (3-aminopropionates (column 8, lines 57-60). Also, Niemiec teaches the use of amphoteric surfactants such as cocamidopropyl betaine in compositions containing diltiazem (paragraphs [0097], [0100], [0101] and [0171] and claims 16 and 17)."

However, Applicants respectfully disagree with Examiner's analysis. The Examiner is again reminded that in an obviousness analysis, as we noted above, the Examiner must unequivocally articulate that the prior art teaches and/or suggests the claimed invention such that one of ordinary skill in the art is motivated to make such a modification to arrive at the invention at issue at the time Applicants made the invention. That is, as stipulated by KSR and the new office guidelines as delineated above - "Combining prior art elements according to known methods to yield predictable results," - the Examiner must show:

(1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

(2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately; and

(3) a finding that one of ordinary skill in the art would have recognized that the ***results of the combination predictable***. (emphasis added)

Again, as we discussed above, none of the references either taken alone or in any combination thereof does not satisfy requirement one above. That it is again reiterated that none of the references, Heinicke (as specifically conceded by the Examiner for certain elements), Baichwal and further in view of Niemiec (which is again not available as a prior art) teach or suggest a "delayed release coated core which produces a timed pulse release containing an active substance in its core" as presently taught and claimed in the instant invention. Thus it is submitted again that the Examiner has not met the burden of establishing prima facie case of obviousness.

In view of the foregoing, it is respectfully submitted that rejection as to claims 1, 3, 6-9 and 11-18 be withdrawn.

Claims 1, 3, 7-9, 11-22, 25-33 and 35 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Andrieu et al. (US 5,589,190) in view of Wilson et al. (6,403,597) and further in view of Smith et al. (US 5,922,341).

In particular the Examiner alleges that "Andrieu discloses pharmaceutical composition comprising alfuzosin hydrochloride core that is coated with methacrylic acid copolymer (EUDRAGIT S) (abstract; column 1, line 51). The formulation comprises tablets that afford immediate or sustained release or microparticles that provide immediate release of alfuzosin (columns 1-3 and claims 1-10). EUDRAGIT S is type B such that Andrieu meets claims 1 and 3. The tablet of Andrieu contains microparticles of polyvinylpyrrolidone in the core with the alfuzosin (column 1, lines 34-46 and Examples 1-3) meeting claims 8, 9, 13 and 14 and in the absence of factual evidence/unexpected results/unusual results, the recited particle size is not inventive over the particles of Andrieu ; the presence of the pyrrolidone meets claims 11 and 12 while the coated core meets the requirements of claims 1 and 13. Example 3 describes a capsule dosage form

that contains multiple forms, immediate and delayed/sustained release forms, meeting claim 19-22, 25-28 and 35. Claims 15-17 are product by process claims such that the dosage of Andrieu meets the product of claims 15-17. Claim 18 recites the properties of the dosage form.

Wilson teaches sustained release (column 7, line 63) composition that contains active agents, excipients, surfactants and optional enhancer (abstract; column 5, lines 34-41). The primary active agent is a phosphodiesterase inhibitor (column 8, lines 36-42). A variety of other agents are administered with the inhibitor (column 11, lines 49); the composition is formulated into tablets that contain binders such as polyvinylpyrrolidone to ensure that the tablet remains intact (column 15, 5-15), anionic or cationic or amphoteric or non-ionic surfactants (column 15, lines 5 and 33-35). The composition of Wilson also contains organic acids such as oxalic acid, fumaric acid, malic acid, tartaric acid and citric acid (column 13, lines 64-67). Alfuzosin is one of the few adrenergic antagonists listed at column 12, lines 37 and 40. Similarly, Smith discloses sustained release dosage form that comprises alfuzosin adrenergic antagonist (column 5, lines 55 and 58), organic acid such as maleic acid, fumaric acid, tartaric acid, citric acid or succinic acid (column 6, lines 23-28), and amphoteric surfactant (column 7, lines 62-64).

Andrieu fails to teach the presence of surfactant in the alfuzosin formulation. However, Wilson and Smith teach formulations that comprise alfuzosin and amphoteric surfactant (abstract; column 5, lines 39-44; column 6, 1-5 and column 12, line 40). Wilson and Smith are thus relied upon for the teaching that alfuzosin formulations can have zwitterionic/amphoteric surfactants. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare alfuzosin formulation as disclosed by Andrieu. One having ordinary skill in the art would have been motivated to incorporate amphoteric surfactant in the alfuzosin formulation with the expectation that the presence of the surfactant would facilitate the dissolution of alfuzosin."

Here again, Applicants respectfully disagree with Examiner's analysis because of the same reasons advanced above. That is, Andrieu et al., Wilson et al., or Smith et al. taken alone or in any combination do not teach or suggest a "delayed release coated core which produces a timed pulse release containing an active substance in its core" as presently taught and claimed in the instant invention. Thus it is submitted again that the Examiner has not met the burden of establishing prima facie case of obviousness.

In view of the foregoing, it is respectfully submitted that rejection as to claims 1, 3, 7-9, 11-22, 25-33 and 35 be withdrawn.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1, 3, 6-9, 11-23, 25-33 and 35 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

As noted above, Applicants concurrently submit herewith a petition for one-month extension of time to make this response timely. Applicants request the Commissioner to charge these fees and any other fees that are deemed necessary due to this submission to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

Respectfully submitted,

October 11, 2007

Balaram Gupta

Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

sanofi-aventis U.S. LLC
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626